Neuropathology of DRUG ADDICTIONS AND SUBSTANCE MISUSE

General Processes and Mechanisms, Prescription Medications, Caffeine and Areca, Polydrug Misuse, Emerging Addictions and Non-Drug Addictions

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Chapter 89

Kratom (*Mitragyna speciosa*) Use, Addiction Potential, and Legal Status

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Abbreviations

CNS	Central nervous system
DEA	US Drug Enforcement Agency
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
KDS	Krathom Dependence Scale
NIH	National Institutes of Health
ROA	Route of administration
δ	Delta opioid receptors
μ	Mu opioid receptors

INTRODUCTION

Kratom (mitragynine) is a botanical-based psychoactive drug derived from the *Mitragyna speciosa* plant indigenous to South East Asia. It has long been available in Thailand, the Philippines, Myanmar, and New Guinea and is increasingly available worldwide through the Internet (Rosenbaum, Carreiro, & Babu, 2012; Sharma, Schifano, & Feinmann, 2011). Other names for the psychoactive derivative of the plant include biak, ketum, krathom, kakuam, ithang, or thom (Thailand), biak-biak or ketum (Malaysia), and mambog (Philippines) (EMCDDA, n.d.; DEA, 2013). The botanical classification of the plant from which Kratom is produced (*M. speciosa*) is in the coffee plant Rubiaceae family, the *Mitragyna* genus, and the *speciosa* species. There are four *Mitragyna* species (*M. speciosa*, *Mitragyna hirsuta*, *Mitragyna diversifolia*, and *Mitragyna rotdifolia*); however, *M. speciosa* is the plant that is primarily used to produce Kratom. The *M. diversifolia*, *M. hirsuta*, and *M. rotdifolia* species are also used but are reportedly less effective (Sukrong et al., 2007). *M. speciosa* is a leafy tree (3–15 m high) that grows wild in marshy areas in Asia and is most prolific in Thailand, Malaysia, Borneo, and New Guinea. Kratom is a psychoactive compound (drug) found in the leaves of *M. speciosa*. It can be consumed in fresh, dried (leaf or powder), or concentrated liquid extract form. The use of *M. speciosa* as a narcotic is not new; however, the extraction and refinement of the alkaloids from the plant into Kratom is relatively neoteric.

CHEMISTRY

More than 25 alkaloids have been isolated in *M. speciosa*. The chemistry of its alkaloids began to be identified in the early 1900s and mitragynine was isolated in the early 1920s (Field, 1921; Grewal, 1932). Plant alkaloids are naturally occurring nitrogen-based substances that are a product of plant metabolism. Many plant alkaloids have psychoactive properties (e.g., alkaloids in the coca plant are used to produce cocaine; morphine is a biosynthesized alkaloid from the opium poppy). The alkaloids that are believed to be primarily responsible for Kratom's psychoactive properties are mitragynine, mitragynine hydroxyindolenine (7-hydroxymitragynine), and mitragynine pseudoindoxyl.

There are several molecular formulas for Kratom depending on the specific plant species used and the alkaloid formulation from the plant. The molecular formula for mitragynine is $C_{23}H_{30}N_2O_4$, and its chemical name is 9-methoxy-corynantheidine (see Figure 1(A) for image of structural analog). Closely related is speciociliatine, with the same molecular formula $C_{23}H_{30}N_2O_4$ but different chemical structure and name, 17-didehydro-9 (see Figure 1(B)). Paynantheine's molecular formula is $C_{23}H_{28}N_2O_4$ (see Figure 1(C)). The formula for mitragynine hydroxyindolenine is $C_{23}H_{30}N_2O_5$ and its chemical name is 7-hydroxymitragynine (see Figure 1(D)). The formula for another common alkaloid extract from this plant, called corynantheidine, is $C_{22}H_{28}N_2O_3$ (see Figure 1(E)). Figure 1(A–E) are structural analogs constructed using PubChem Compound Summary from the National Center for Biotechnology Information, US National Library of Medicine (NCBI, 2014). These chemicals operate on opiate receptors and produce similar effects to heroin ($C_{21}H_{23}NO_5$); however, the chemical structure of heroin, which is displayed in Figure 1(F), is different.

Kratom produces both stimulant and depressant effects in the central nervous system (CNS). At low doses, Kratom has stimulant effects and is used to combat fatigue. However, at higher dosages it can have sedative-narcotic effects and operates on the opioid receptors (Kapp, Maurer, Auwärter, Winkelmann, & Hermanns-Clausen, 2011). It has long been used in traditional medicine and more recently worldwide as an opium substitute, including for treatment of opioid withdrawal. Mitragynine is responsible for the opioid-like effects of Kratom, and is a partial agonist of the μ (mu) and δ(delta) opioid receptors, which may account for its apparent efficacy in treating opiate withdrawal (Rosenbaum et al., 2012). The μ receptor mediates analgesia, euphoria, and respiratory depression, which accounts for the analgesic effects of mitragynine and its ability to amelioration opiate withdrawal symptoms

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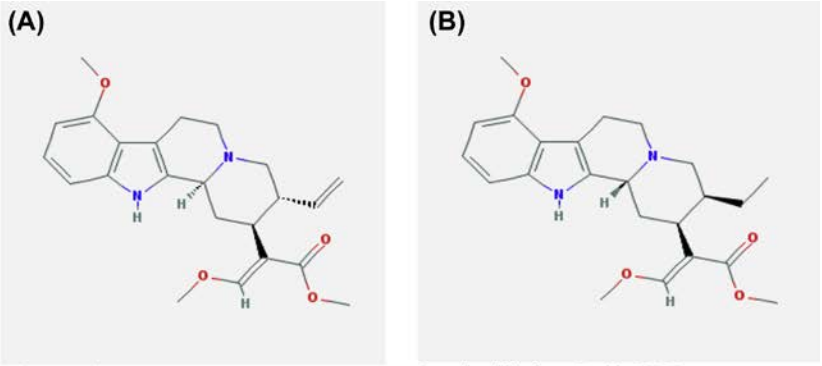
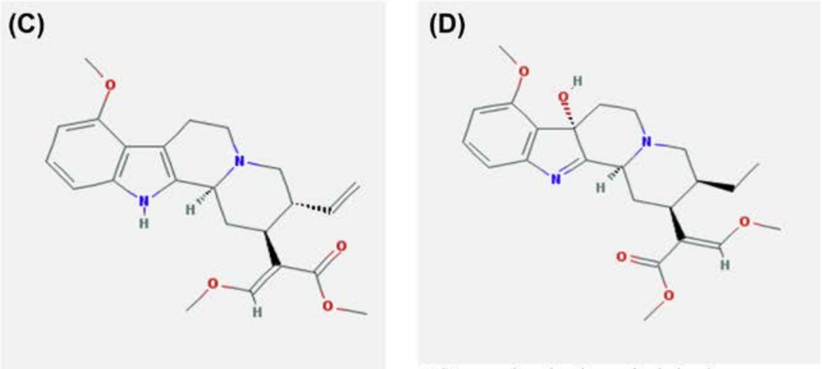
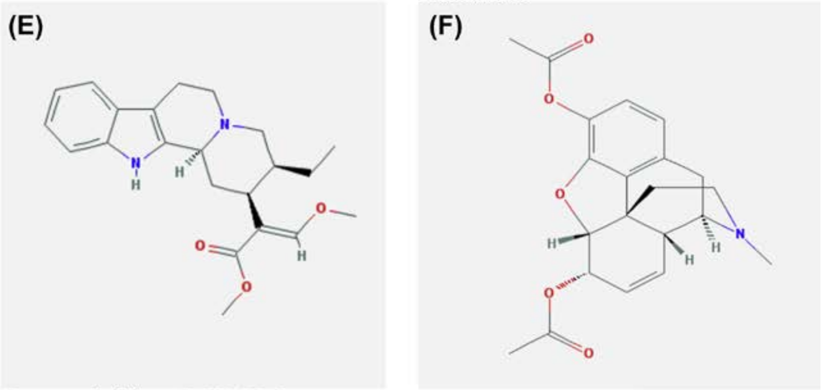


Mitragynine $C_{23}H_{30}N_2O_4$ Speciociliatine $C_{23}H_{30}N_2O_4$



Paynantheine $C_{23}H_{28}N_2O_4$ Mitragynine hydroxyindolenine $C_{23}H_{30}N_2O$



Corynantheidine $C_{22}H_{28}N_2O_3$ Heroin $C_{21}H_{23}NO_5$

FIGURE 1 **(A–E) Chemical structures of psychoactive compounds derived from the *Mitragyna speciosa* plant. (F) Chemical structure of heroin.** These chemical compounds were created with PubChem Compound Summary from the National Center for Biotechnology Information, US National Library of Medicine (NCBI, 2014).

(Boyer, Babu, Adkins, McCurdy, & Halpern, 2008; Boyer, Babu, Macalino, & Compton, 2007; Boyer, McCurdy, & Adkins, 2010).

PREVALENCE OF USE

In Thailand, Kratom (*Mitragyna*) is reportedly used primarily among the working class. Historically, *M. speciosa* has been used by humans regionally in South East Asia. More recently, its use has spread throughout Australia, Europe, and North America, and it is accessible via the Internet without a prescription in many countries. The availability and trade of Kratom in Europe, Australia, and the United States emerged at the turn of the twenty-first century, primarily through proliferation of information on the Internet about the drug coupled with Internet sale and global marketing of the drug. The use of Kratom in its more natural form as a plant preparation in its countries of origin is associated with lower addiction and health problems; however, the extraction of more potent and purified alkaloids has greater addiction potential (e.g., coca leaves vs cocaine hydrochloride) (Hassan et al., 2013; Streatfeild, 2001; Takayama, 2004).

A National Household Survey of drug use in Thailand found that the lifetime prevalence of Kratom use among the Thai population (ages 12–65) was 2.3%, past year use was 0.8%, and past 30-day prevalence was 0.6% (Assanangkornchai, Muekthong, Sam-angsri, & Pattanasattayawong, 2007). A study of Thai youth

(13–16 years old) revealed notably higher lifetime use of Kratom with a substantial increase from 4% in 2002 to 9.4% in 2004 (Assanangkornchai, Pattanasattayawong, Samangsri, & Mukthong, 2007). Data on prevalence of Kratom use outside of Thailand is very limited and not regularly tracked. In 2008 the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) conducted a survey of 27 European online sites selling "legal highs" and found that Kratom was one of the most widely offered drugs available on 44% of the sites investigated (EMCDDA, n.d.; Spring, 2009). The US Drug Enforcement Agency (DEA, 2005) released a report on Kratom, which noted that because Kratom use and abuse is not monitored by any national survey, law enforcement, or systematic process, the extent of its use in the United States is not known. Kratom's wide availability on the Internet suggests that demand is extensive. Reports of Kratom abuse have been published in Great Britain, Germany, Malaysia, and Thailand (DEA, 2005; Kronstrand, Roman, Thelander, & Eriksson, 2011; McWhirter & Morris, 2010; Nelsen, Lapoint, Hodgman, & Aldous, 2010; Ulbricht et al., 2013).

The authors of this chapter conducted a review of available scholarly literature about Kratom, mitragynine, and articles referencing both Kratom and mitragynine. Our research revealed 951 publications that mention Kratom through Google Scholar and PubMed/Medline; of these over 50% ($n = 554$) were published between 2011 and 2014. A search of literature referencing mitragynine revealed 810 publications through Google Scholar. A literature search through the US National Library of Medicine National Institutes of Health database PubMed/Medline for all years produced just 56 publications referring to Kratom. The prevalence of scholarly publications by year is presented in Figure 2.

KRATOM ABUSE AND ADDICTION

Research on people who are categorized as regular Kratom users (≥6 months of use) with mean daily intake of ~276 mg of Kratom in drink form (~79 mg/drink) has found evidence of psychological and physical dependence on Kratom. Cessation of Kratom use produced physical withdrawal symptoms similar to opiate addiction including pain, muscle spasms, sleep difficulty, watery eyes, runny nose, hot flashes, fever, decreased appetite, diarrhea, and Kratom craving. Psychological withdrawal symptoms reported by users included restlessness, tension, anger, and depression (Singh, Müller, & Vicknasingam, 2014). The Krathom Dependence Scale (KDS) was developed by Saingam and colleagues as a reliable and valid instrument to identify Krathom (Kratom) users' potential dependency. The KDS contains 16 items with a 0–3 rating scale, for a potential total score of 0–48. A score of 13–33 indicates moderate dependence whereas a score of 34/35 or higher indicates high dependence (Saingam, Assanangkornchai, Geater, & Lerkiatbdit, 2014).

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCES OF ABUSE

Kratom for Opiate Withdrawal

With the intensifying potency of Kratom, its addiction potential also increases.

Concomitant with reported concerns of Kratom toxicity, tissue dependency, and addiction, this substance is also being researched for use as a potential treatment for opiate addiction.

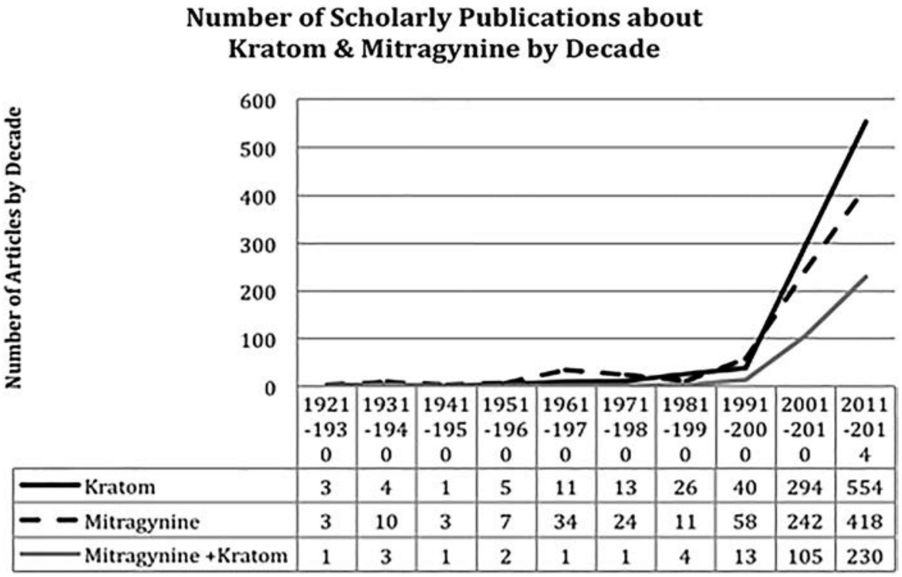
The National Institutes of Health (NIH) has funded research on Kratom as a potential treatment for weaning people from opiate and opioid addiction. Dr Edward Boyer, at the University of Massachusetts School of Medicine, and Dr Christopher McCurdy in the School of Pharmacy at the University of Mississippi have isolated mitragynine alkaloids and tested their efficacy in managing opiate withdrawal in animal studies. Boyer's research reported that it is superior to methadone in withdrawal assay tests with animals (Boyer et al., 2007, 2008). Research using Kratom in tea formula found that mitragynine fully blocked opiate withdrawal symptoms suggesting it may be an effective substitute for weaning people addicted to opiates (morphine, oxycodone, heroin) through a step-down treatment (Ward, Rosenbaum, Hernon, McCurdy, & Boyer, 2011). Replacement therapy drugs such as methadone, suboxone, or subutex require long-term use for opiate withdrawal maintenance; however, Kratom appears to hold promise as an effective means of fully withdrawing humans from opiate dependence (Ward et al., 2011). Kratom has a history of use in South East Asia to reduce addiction to other drugs, which are often more expensive, and to manage opiate withdrawal symptoms (Vicknasingam, Narayanan, Beng, & Mansor, 2010).

ROUTES OF ADMINISTRATION

Kratom leaves can be chewed or they can be refined into powder and liquid extract form. The leaves differ greatly in potency, depending on the type, grade, and freshness. The color of the veins in the leaves also differentiates the subtypes of *M. speciosa*. The green vein leaves are reportedly stronger than the red vein leaves; however, there is some contradictory evidence in the literature regarding the strength of differing leaves (Sukarong et al., 2007).

When chewed fresh, half of a large leaf (23 cm or 9 inches) is reported to be a quantity sufficient to produce noticeable effects. In Thailand, Kratom is also consumed as a "beverage" called "4X100" when combined with cola and cough syrup containing codeine or diphenhydramine (Greenemeir, 2013). Some preparations include the addition of an anxiolytic, antidepressant, or analgesic drugs, which increase the risk of the drink having potential lethality due to multidrug interactions (stimulants, depressants) (Tanguay, 2011; Tgtananuwat & Lawanprasert, 2010).

According to interviews with Kratom users that were conducted by the authors of this chapter, Kratom is available in the United States through "head shops" (a.k.a. smart shops), online retailers, ethnobotanical merchants, and from dealers on the street. Multiple brands and strains of *M. speciosa* are available from different retailers. Although Kratom is legal throughout most of the United States, there have been precautions taken by head shops to decrease the visibility of Kratom in their stores for protection from governmental interests and the rapidly changing legal status of *M. speciosa*-related chemical compounds. The popularity of Kratom in most of the United States is moderate to low and therefore the head shops end up with stale varieties of Kratom to purchase. As of 2013 vials of liquid Kratom, like item A in the photograph in Figure 3, were available for sale in head shops in the United States; however, by 2014 this specific formula of Kratom described by our interview subject was no longer available in stores. The change in availability of this particular formula was because of precautionary measures taken by the distributor and the shop for legal



	1921-1930	1931-1940	1941-1950	1951-1960	1961-1970	1971-1980	1981-1990	1991-2000	2001-2010	2011-2014
Kratom	3	4	1	5	11	13	26	40	294	554
Mitragynine	3	10	3	7	34	24	11	58	242	418
Mitragynine +Kratom	1	3	1	2	1	1	4	13	105	230

FIGURE 2 **Numbers of scholarly publications about Kratom 1920–2014.** This graph illustrates the number of scholarly articles published about Kratom each decade dating back to 1920. The number of articles published from 2010 to 2014 demonstrates a significant increase in research and scientific interest in Kratom.

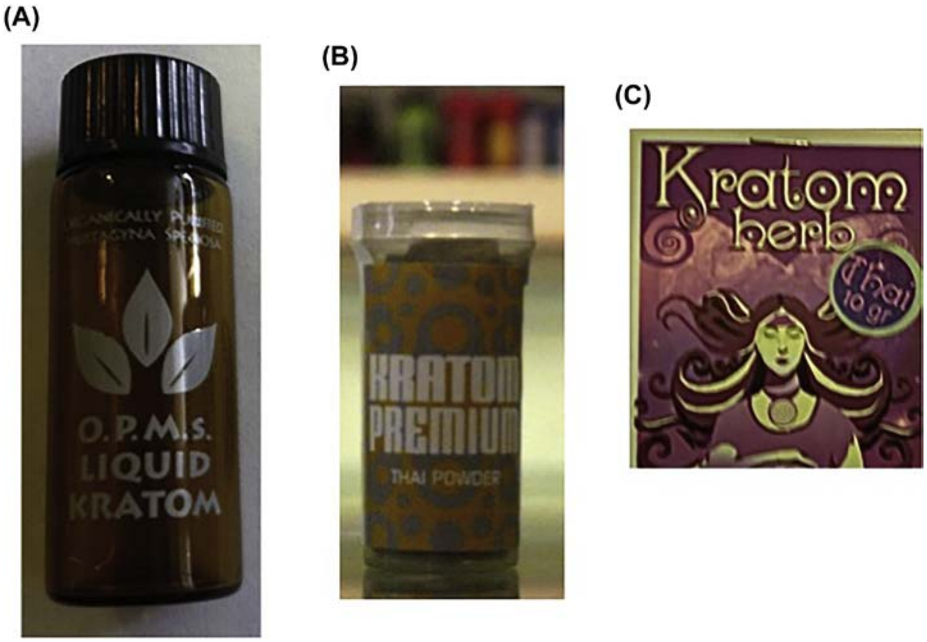


FIGURE 3 **Photographic images of Kratom as legally sold in the United States and Europe.** (A) Liquid Kratom legally purchased in the U.S., (B) and (C) Powder Thai Kratom legally purchased in the Netherlands. *Photography credits Kendra MacClurg and Dessa Bergen-Cico.*

protection in response to changing laws regarding certain specific chemical compounds in Kratom. Users described the liquid Kratom in the vial depicted as item A in the photograph as bitter and smooth. Kratom that is available now is less concentrated, and powdered Kratom is the most widely available form. Powdered Kratom can be mixed into teas and drink mixtures, which results in a gritty feeling when consumed. Premixed Kratom drinks are marketed in small 60-g (~1.5-ounce) containers. As of 2014, liquid and powdered Kratom were available in "smart shops" in the Netherlands. Images of the liquid and powdered Kratom products available in Europe are depicted in the photographs in Figure 3 and labeled as items B and C.

TABLE 1 Dosing Effects of Kratom Powder

Dose	Reported Typical Effect[a]
2–6 g	Mild effects; typically effects are stimulant-like at this level
7–15 g	Medium strength effects; effects can be stimulant-like or sedative-euphoric-analgesic
16–25 g	Strong effects (sedative-euphoric-analgesic effects); considered too strong for people sensitive to drug effects
Above 26 g	Very strong sedative-euphoric-analgesic effects; considered too strong for most people

[a] *Effects are based on compilation of reports of effects by users gathered through author interviews and advice sites for users as written by Kratom users.*

DOSING AND EFFECTS

According to interviews conducted by the authors of this chapter, users who have addictions to heroin and opiate medications may turn to Kratom as a substitute or means of managing withdrawal. Kratom is not a drug that shows up on current drug test results and allows users to continue attaining the opiate effects even when participating in programs or rehabilitation that prohibit the use of opiates without a prescription. Individuals who have used Kratom as a replacement for other opiate substances report that with high doses, the effects of Kratom are similar, although to achieve these effects large amounts of Kratom need to be purchased. Depending on the retailer, the price range of Kratom capsules and powder begins with small quantities at €12 (=£9, $15) and increases exponentially as the amount of Kratom is increased. According to interviews conducted by the authors of this chapter, five capsules of Kratom cost about €35 (=£28, $45).

Dosages can vary greatly depending on the freshness of the leaf and the potency of the particular plant and strain. Fresh Kratom and freshly dried leaves are considered most potent. Dried leaves and powder are most common outside of regions where the plant grows naturally in South East Asia. However, the lack of regulation and control over such herbal drugs, marketed in head/smart shops and on the Internet, cannot ensure their composition or purity and represent a serious hazard to public health. One study that tested Kratom products available online and in head/smart shops found varying potency and purity of Kratom products (Carnara et al., 2013).

The dried form of Kratom is sold as straight-up dried leaf, powder, capsule, and prepackaged tea bags. Low doses are around 2–3 g of plain dried leaf, moderate doses are 4–6 g, and strong doses are 7 g or more. Its leaves contain mitragynine and when chewed they act as a stimulant (low dose) or an opiate substitute (higher doses). Effects typically begin within 5–10 min after ingestion when leaves are chewed, and effects are reported to last 1–5 h (Apryani, Taufik Hidayat, Moklas, Fakurazi, & Farah Idayu, 2010). Medical researchers report that adverse reactions to Kratom use include nausea, vomiting, and diarrhea, with some reports of nystagmus and muscle tremors. Moreover, because Kratom has low toxicity, treatment of these side effects and symptoms is adequate (Babu, McCurdy, & Boyer, 2008; Boyer et al., 2008).

Individuals who chronically use Kratom exhibit symptoms consistent with chronic use of stimulants and some opiates, including but not limited to weight loss, dry mouth, and constipation. There are also reports of darkening skin patches particularly on the cheeks. Withdrawal symptoms can include muscle and joint pain, hostility, aggression, watery eyes, and muscle spasticity. Kratom dosing levels that are high enough to produce depressant effects and then combined with other CNS depressants such as alcohol, barbiturates, and opiates (including heroin and synthetic opioid pharmaceuticals such as Fentanyl, Subutex, Oxycontin) increase the risk of respiratory depression, which can stop breathing and be fatal. Fatal cases of intoxication associated with the use of Krypton, a mixture of mitragynine and *O*-desmethyltramadol, have been described in the scientific literature (Forrester, 2013). However, these fatalities have been attributed to the addition of *O*-desmethyltramadol to the dried Kratom leaves (Kronstrand et al., 2011) (Table 1).

PRICE

A 2011 study conducted by Schmidt and colleagues examined the pricing and availability of Kratom on 314 online sites selling “legal highs” and reported price ranges for dried Kratom of €6–15 (=£4.70–11.70, $7.60–19) per 10 g (=0.35 ounce) and €7.50 (=£5.50, $9) per gram of “Kratom 15X” in extract form (Schmidt, Sharma, Schifano, & Feinmann, 2011). A report from the DEA stated that dried Kratom leaves were selling for €8–31 (=£6–24, $10–40) per ounce (=38 g) in the United States. Kratom leaves (fresh and dried) and plants are widely available on the Internet and may be sold at some head shops in the United States (DEA). Our 2014 review of websites selling Kratom online reveal websites selling powdered Kratom (commercial grade White Vein Thai, Green Malaysian, and Bali) for as little as €4.70 (=£3.70, $6) per ounce (=38 g). From sites selling within the United States high-quality Maeng Da Kratom is sold for €6–14 (=£511, $818) per ounce (=38 g).

LEGAL STATUS

Until recently, Kratom and its primary psychoactive alkaloids were legal worldwide. In 2003 it became illegal in Malaysia, and it is presently illegal in Thailand, where its legal status has changed several times since the 1940s. Currently, neither Kratom, *M. speciosa*, nor mitragynine or other alkaloids from the plant are listed under the 1961 or 1971 Schedules of the United Nations Drug Conventions; therefore, its legal status is independently established by each country, state, or region (Hillebrand, Olszewski, & Sedefov, 2010; UNODC, 2012, 2013). However, *M. speciosa*, mitragynine, and 7-hydroxymitragynine are currently controlled in several European countries, many South East Asian countries, and some parts of the United States. Please refer to Table 2 for the legal status of *M. speciosa*, mitragynine, and their derivatives as of 2014. Countries

TABLE 2 Legal Status of Kratom as of December 2014

Country	Status	Details
Austria[a]	Legal	
Australia[a,b]	Restricted	Both mitragynine, one of the active chemicals in kratom, and *M. speciosa* were placed in Schedule 9 of the Australian SUSDP in 2005
Belgium[a]	Legal	
Burma[b]	Controlled	
Denmark[a]	Controlled	
Finland[a]	Controlled	Requires a prescription. Shipments can be seized at the border
Germany[a]	Controlled	Controlled as an approved pharmaceutical drug
Hungary[a]	Legal	Not approved for human consumption, but available as incense in head shops
Latvia[a]	Controlled	
Lithuania[a]	Controlled	
Malaysia[b,c]	Illegal	Controlled under narcotic law
Myanmar[a]	Illegal	Controlled under narcotic law
The Netherlands	Legal	Available in smart shops (head shops)
New Zealand	Controlled, restricted	*M. speciosa* and mitragynine controlled under Schedule 1 of the Medicines Amendment Regulations 2009 (SR 2009/212 prescription, restricted, and pharmacy-only medicines). Not legal to sell Kratom without a license, though not illegal to possess
Poland[a]	Controlled	
Romania[a,b]	Controlled, illegal	
Russia[d]	Illegal	Mitragynine (9-methoxy-corynantheidine) and its derivatives are illegal[2a]
Sweden[a]	Controlled	
South Korea[b]	Illegal	
Thailand[a,e]	Illegal Thailand is considering making Kratom legal again in an effort to find safer healthier stimulants to combat Thailand's high rate of methamphetamine addictions	Illegal to buy, sell, import, or possess. Exceptions are made with permission from the Minister of Public Health in accordance with approval from the Office of the Narcotics Control Board
United Kingdom[a]	Legal	Sold in head shops (smart shops)
United States	Varying regulation Legal or regulated in most states	Banned in Indiana State.[f] Louisiana State[g] prohibits distribution of products containing *M. speciosa* to minors (under age 18). Tennessee State[h] is controlled and illegal to sell. In 2005 the DEA listed this as a drug of concern with abuse potential.[i] As of 2014 Kratom is not a scheduled or restricted drug on the federal level
Vietnam[b]	Controlled	

SUSDP, Standard for the Uniform Scheduling of Drugs and Poisons; DEA, US Drug Enforcement Agency; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction.

[a] *EMCDDA,*

[2a] *EMCDDA (n.d., 2012).*

[b] *Ancuceanu et al. (2010).*

[c] *Malaysia Section 30 (3) Poisons Act 1952.*

[d] *Russian Federation, Decision No. 822 (2011), Translation of Russian documents provided by Alexei Chingin.*

[e] *Thailand Kratom Act 2486 of 1943.*

[f] *Indiana Senate Bill No. 305 (2014).*

[g] *Louisiana Senate Bill No. 130, Act No. 355 (2012).*

[h] *Tennessee House Bill No. 12, Section 39-17-452(a)(2), Section 6.*

[i] *DEA (2005, 2013).*

not listed in Table 2 could not be verified for legal status through primary sources. As of the writing of this chapter Kratom is legally available at some head shops and online in several European countries (e.g., the United Kingdom and the Netherlands) and 47 of 50 states in the United States. Kratom is also widely available on the Internet in the form of leaves (whole or crushed), powder, extract, encapsulated powder, and extract resin "pies" (40-g pellets made from reduced extract) (DEA, 2005, 2013; Roche, Hart, Sangalli, Lefberg, & Bayer, 2008).

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

At high dosage levels of intake, Kratom acts as a depressant and may produce cross-tolerance with other depressant drugs, most notably opioids and opiates. There is evidence of a relationship between the use of Kratom and opiates, particularly heroin. Kratom is being researched as an effective replacement therapy for people addicted to prescription opioids, heroin, and opium. Some research suggests that it may be more effective than existing pharmaceutical replacement therapies, such as methadone and Subutex, in treating withdrawal symptom management. There is evidence that Kratom is already being used by people in certain parts of the world as a means of self-treatment or symptom management for opiate addiction. Beyond the potential beneficial use of Kratom to treat opiate addiction, there is also some evidence that Kratom itself can be abused and may be addictive. When consumed in higher doses, Kratom operates similarly to, and acts on the same receptor sites as, opium and heroin. At lower levels of intake, Kratom has a stimulant effect and may produce cross-tolerance with other stimulant drugs. It may also be a less toxic alternative to methamphetamine for people abusing methamphetamine. Kratom is increasingly available through online outlets and as such its purity cannot be guaranteed or well regulated. When sold through unregulated markets, such as online outlets, there is increased potential for marketing of synthetic "legal highs" such as Spice, K2, bath salts, etc.

DEFINITION OF TERMS

Controlled drug Drugs categorized as controlled substances (including drugs that may or may not have licit approved medical purposes) are legal for use but have restrictions regarding age of legal use and purchase of the drug; legal restrictions as to whom can sell the substance; and general restrictions over the quantity that can be sold to any one person in a given timeframe. The production, sale, and use of Kratom are controlled in some states and countries. It is not regulated or controlled under international law.

Kratom A plant with psychoactive properties. At low doses it has stimulant effects on the CNS and it is used to combat fatigue. At higher dosages it has sedative-narcotic effects on the CNS and operates on opioid receptors.

Illegal drug Drugs that are under international, state, or federal control (drugs may or may not have licit or legally approved medical purposes) but which are produced, trafficked, and consumed illicitly or illegally. The production, sale, and use of drugs in these categories generally carry legal consequences for people in possession of the drug. Kratom is illegal in some states and countries; however, it is not illegal or illicit according to international law.

Mitragyna speciosa There are four primary types of the *M. speciosa* plant: (1) *M. speciosa*, (2) *M. hirsuta*, (3) *M. diversifolia*, and (4) *M. rotdifolia*.

Mitragynine Includes mitragynine and mitragynine hydroxyindolenine, which are the chemical names for the primary psychoactive compound in the *M. speciosa* plant. Kratom is a street name for substances containing mitragynine and mitragynine hydroxyindolenine.

Routes of administration (ROA) Refers to the method used to ingest or administer a drug into the body. ROA is determined primarily by the properties of the drug (e.g., liquid, dried leaf, powder). The most common ROAs for recreational drugs in descending order of speed of effect are (1) inhalation (smoke), (2) intravenous (injected directly into the blood stream), (3) insufflation (snorted or sprayed up the nose), (4) oral (swallowed by mouth), and (5) transdermal (absorbed through the skin).

KEY FACTS

Key Facts of Kratom

Kratom, also known as mitragynine, is a plant indigenous to South East Asia, which has psychoactive properties. At low doses it has stimulant effects on the CNS. Labor workers in South East Asia have traditionally used (chewed) Kratom to combat fatigue. At higher dosages, Kratom has sedative-narcotic effects on the CNS and it operates on opioid receptors producing opiate (heroin)-like effects.

Key Facts of Kratom Methods of Use

Kratom can be ingested or administered in various forms based on the properties of the drug (e.g., liquid, dried leaf, powder, or paste). The most common methods of use for Kratom are (1) inhalation (smoked from a paste), (2) oral (swallowed as liquid concentrate or powder mixed into beverage), (3) oral (prepared from dry leaves as tea), and (4) oral (chewed as fresh leaf).

Key Facts of Kratom and Alkaloids

Plant alkaloids are naturally occurring nitrogen-based substances that are a product of plant metabolism, and more than 25 alkaloids have been isolated in *M. speciosa*. Many plant alkaloids have psychoactive properties. The alkaloids that are believed to be primarily responsible for Kratom's psychoactive properties are mitragynine, mitragynine hydroxyindolenine (7-hydroxymitragynine), and mitragynine pseudoindoxyl. The extraction of more potent and purified alkaloids from *M. speciosa* has increased Kratom's addiction and abuse potential.

Key Facts of Kratom and Opiate Withdrawal

Concurring with reported concerns of Kratom toxicity, tissue dependency, and addiction, Kratom is also being researched for use as a potential treatment for opiate addiction. Mitragynine is responsible for the opioid-like effects of Kratom. The NIH has funded research on Kratom as a potential treatment for weaning people from opiate and opioid addiction. Research using Kratom in tea formula found that mitragynine fully blocked opiate withdrawal symptoms suggesting it may be an effective substitute for weaning people addicted to opiates (morphine, oxycodone, heroin) through a step-down treatment.

Key Facts of Kratom Legal Status

Until recently, Kratom and its primary psychoactive alkaloids were legal worldwide. As of 2014, Kratom is illegal in the following countries: Malaysia, Myanmar, Romania, Russia, and South Korea. Currently, neither Kratom, *M. speciosa*, nor mitragynine or other alkaloids from the plant are listed under the 1961 or 1971 Schedules of the United Nations Drug Conventions; therefore, its legal status is independently established by each country, state, or region.

SUMMARY POINTS

- The legal status and control of *M. speciosa* and its derivatives, namely, Kratom, vary widely across countries. Currently, it is most restricted in South East Asia where it is indigenous. These chemical compounds are listed under the Schedules of the United Nations Drug Conventions; therefore, its legal status is independently established by each country, state, or region.
- There is limited research evidence on pharmacological, toxicological, neurophysiological, and behavioral effects of Kratom and *M. speciosa*-derived compounds.
- At low doses, Kratom produces stimulant-like effects, similar to those that are achieved by chewing coca leaves.
- At higher doses, Kratom produces depressant effects similar to opiates.
- The addiction potential of Kratom increases with higher doses of consumption, particularly when consumed in forms created through refined synthesis from alkaloid extractions of pure mitragynine and *M. speciosa* preparations.
- Research on the use of Kratom to effectively treat opiate addiction has shown great promise of its efficacy in reducing opiate withdrawal symptoms.
- Interest in the study of Kratom has grown exponentially in recent years as evidenced by the significant increases in scholarly articles published.

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